REMARKS/ARGUMENTS

Claims 119-123 have been amended with the recitation "native sequence polypeptide" support for which is found at least on page 304, line 26 of the instant specification.

Claims 119-126 and 129-131 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §§101 and 112, First Paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-126 and 129-131 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree.

Arguments

The Utility Guidelines were discussed in the previous response filed August 1, 2005. Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed 'native sequences' of the PRO1187 polypeptide of SEQ ID NO: 399. Applicants submit that there is a positive correlation for lung cancer and the gene encoding PRO1187 based on the gene amplification data.

However, in the paragraph bridging pages 3 and 4, the Examiner says that "(t)he PRO1187 **gene** has not been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such" (Emphasis added). The Examiner further adds on Page 4, line 5 of the Office action that "all that the specification does is present evidence that the DNA encoding PRO1187 is amplified in a variety of samples and invites the artisan **to determine the significance of this increase**" (Emphasis added). Applicants strongly disagree.

Table 9C of the instant specification clearly indicates that PRO1187 showed approximately 1.17-1.55 ΔCt units which corresponds to $2^{1.17}$-$2^{1.55}$- fold amplification or **2.25-fold to 2.928-fold** amplification in squamous cell carcinomas of the lung (see Table 8,

page 546). The Applicants also presented the Goddard Declaration in the previous response that indicated that at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful as a tumor marker. Accordingly, these values would be considered significant and credible by one skilled in the art and therefore, PRO1187 gene amplification has clearly been associated as a marker for squamous cell carcinomas of the lung. No further experimentation is required by the artisan to determine the significance of this increase.

The Examiner indicates on page 5, line 4 of the office Action that "there is no evidence regarding whether or not the **PRO 1187 mRNA or protein levels** are also increase in these tumor samples (emphasis added).

Applicants have submitted ample evidence form the art to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* submitted in the response filed November 8, 2004 collectively teach that in general, gene amplification increases mRNA expression. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis (submitted in the response filed November 8, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Taken together, although there are some examples in the scientific

art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* the Polakis Declaration and the widespread use of array chips, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1187 gene, that the PRO1187 polypeptide is concomitantly overexpressed.

Thus, Applicants submit that they have demonstrated utility for the PRO1187 polypeptide as a lung tumor marker based on gene amplification evidentiary data in the specification, and also based on supportive literature which was available to one of skill in the art at the time of filing.

However, the Examiner maintains that the art, as exemplified by Pennica *et al.,* Konopka *et al.,* Haynes *et al.* doe not show such a correlation and further quotes another reference, Hu *et al.* on page 6 of the Final Office Action and says that "among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease." Applicants respectfully disagree.

A. A *prima facie* case of lack of utility has not been established

First of all, as discussed in the response mailed August 1, 2005, the references cited by the Examiner, namely, Pennica *et al.,* Konopka *et al.,* they do not address general trends or genes "in general" and instead address isolated cases. Also, Haynes *et al.* meets the "more likely than not standard" and in fact support the Applicants position that that a positive correlation exists between mRNA and protein, (see Haynes data (Figure 1)).

And contrary to the Examiner's assertion, the cited Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO1187 molecule for the following reasons. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining." Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in

disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different statistical methods* " were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect *a bias in the literature* to study the more prevalent type of tumor in the population.

Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general.*

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of *one* class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.*, Konopka *et al.*, Haynes *et al.* or Hu *et al.* by the Examiner.

On the other hand, one of skill in the art would reasonably expect, based on: (a) the gene amplification data for the PRO1187 gene, (b) the supportive evidence in the Declarations submitted, and (c) the supportive articles presented by the Applicants which were available in the art at the time of filing of the instant application, that the PRO1187 polypeptide is most likely, concomitantly, overexpressed in certain lung tumors, just like the PRO1187 gene, and is therefore useful as a tumor marker for certain lung cancers. Even in the event that the PRO1187 polypeptide were found not to be overexpressed in the lung tumors where the PRO1187 gene were amplified, (a position expressly not conceded to), the PRO1187 polypeptide is still useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility and enablement rejections should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 119-123 are rejected under 35 U.S.C. §112, first paragraph, because the claimed invention allegedly "fails to comply with the written description requirement." In particular, the Office Action states that " the specification provides adequate written description for SEQ ID NO: 399, but not variants....the instant specification contemplates but does not exemplify variants of the protein.....The specification does not provide any guidance as to what changes should be made and which regions of the instant protein are functionally and structurally critical." Applicants respectfully traverse.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[1,2] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[4,5]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[7] Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8,9]

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[2] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[3] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[5] *See also* M.P.E.P. §2163 II(A).

[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[7] *See also* M.P.E.P. §2141.03.

[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[9] *See also* M.P.E.P. §2141.03.

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO: 399. Applicants also submit that the specification provides ample written support for determining percent sequence identity between two amino acid sequences (See pages 306-308, line 14 onwards). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to the changes that may be made to a PRO polypeptide without adversely affecting its activity (page 372, line 36 to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, one of skill in the art could identify whether the variant PRO1187 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 376, line 9) and methods of preparing the PRO polypeptides (see Examples 140-143).

Currently pending Claims 119-123 recite the functional limitation that the nucleic acid encoding said polypeptide is amplified in squamous cell carcinomas of lung. Applicants further submit that the specification provides ample written support for detecting and quantifying amplification of such nucleic acids in several tumors and/or cell lines as described in Example 170. Example 170 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following this disclosure, one skilled in the art would know that it is easy to test whether a gene encoding a variant PRO1187 protein is amplified in squamous cell carcinomas of lung by the methods set forth in Example 170.

More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in

Enzo was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

Accordingly, current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities. The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An Applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[10] Thus, the genus of polypeptides with at least 80-99% sequence identity to SEQ ID NO: 399, which possess the functional property of having a nucleic acid which is amplified in squamous cell carcinomas of lung would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description. Accordingly, one skilled in the art would have known that Applicants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 399 whose encoding nucleic acids were amplified in squamous cell carcinomas of lung. The recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand.

As discussed above, Applicants have recited structural features, namely, 80% sequence identity to SEQ ID NO: 399, which are common to the genus. Applicants have also provided guidance as to how to make the recited variants of SEQ ID NO: 399, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further

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[10] M.P.E.P. §2163 II(A)(3)(a)

defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

For the above reasons, the specification provides adequate written description for polypeptides having at least 80% identity to SEQ ID NO: 399 wherein the nucleic acid encoding the polypeptide is amplified in squamous cell carcinomas of lung. Accordingly, Applicants respectfully request reconsideration and reversal of the written description rejection of Claims 119-123 under 35 U.S.C. §112, first paragraph.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C40**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 9, 2006

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